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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/576,496

04/20/2006

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Q94468

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23373 7590 02/20/2009  
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EXAMINER

DUNSTON, JENNIFER ANN

ART UNIT

PAPER NUMBER

1636

MAIL DATE

DELIVERY MODE

02/20/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/576,496	<b>Applicant(s)</b> KOMORI ET AL.	
	<b>Examiner</b> JENNIFER DUNSTON	<b>Art Unit</b> 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 14 November 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-7,9,15-22 and 31-38 is/are pending in the application.
- 4a) Of the above claim(s) 1-4,9,15-22 and 31-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 5-7 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 April 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4/20/2006, 5/6/2008</u>                                       | 6) <input type="checkbox"/> Other: _____                          |

Art Unit: 1636

### **DETAILED ACTION**

Receipt is acknowledged of an amendment, filed 9/13/2006, in which claim 30 was canceled, claims 3, 16, 17, 31-36, 39 were amended, and claims 41-94 were newly added.

Receipt is also acknowledged of an amendment, filed 10/27/2006 and 11/9/2006, in which claims 8, 10-14, 23-29 and 39-94 were canceled, and claims 2, 3, 15-18, 20-22, 31, 32, 34, 35, 37 and 38 were amended. Claims 1-7, 9, 15-22 and 31-38 are pending.

### ***Election/Restrictions***

Applicant's election without traverse of Group II in the reply filed on 11/14/2008 is acknowledged.

Claims 1-4, 9, 15-22 and 31-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/14/2008.

An examination on the merits of claims 5-7 follows.

### ***Priority***

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Receipt of the certified copy of the foreign priority document, Japan 2003-359172, is acknowledged. These papers have been placed of record in the file.

### ***Information Disclosure Statement***

Receipt of information disclosure statements, filed on 4/20/2006 and 5/6/2008, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

### *Specification*

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because it contains more than 150 words and includes legal phraseology, such as "means" in line 5. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: the term "Runx2/Cbfa1" is misspelled as "Runx2/Cba1" (paragraph bridging pages 8-9; page 32, last full paragraph; paragraph bridging pages 32-33).

Appropriate correction is required.

The use of the trademarks GENBANK (page 24, 2nd paragraph), ISOGEN (page 62, Example 1, section (4); page 68, Example 4, section (1); page 69, Example 4, section (2)), OLIGOTEX (page 68, Example 4, section (1)), and LIFEARRAY (page 68, Example 4, section (1)) has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Art Unit: 1636

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 7 is drawn to the RU-1 and Ru-22 cell lines derived from a Runx2/Cbfa1- and p53-deficient mouse.

The application discloses cell lines RU-1 and RU-22 that are encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. The specification teaches the

Art Unit: 1636

production of Runx2/Cbfa1- and p53-deficient mice by mating the prior art Runx2/Cbfa1-heterodeficient mice with prior art p53-deficient mice and continuing with the appropriate crosses to obtain the desired deficient mouse (e.g., pages 60-61, Example 1, sections (1) and (2)). The specification teaches the preparation of chondrocyte cell lines derived from Runx2/Cbfa1 -/- and p53 -/- mice (e.g., pages 61-62, Example 1, section 3). The derivation process comprised the following steps: (i) skeletons from Runx2/Cbfa1 -/- and p53 -/- mice at day 18.5 of embryonic development (E18.5) were treated with a solution containing 0.1% EDTA and 0.1% Trypsin (pH 7.4) at 37°C for 60 minutes; (ii) skeletons were treated with 1.5 mg/ml collagenase and alpha modified-minimum essential medium ( $\alpha$ MEM) for 3.5 hours to obtain a cell suspension; (iii) the resulting cells were cultured on a dish containing 10% fetal bovine serum (FBS) and Dulbecco's Modified Eagle's Medium (DMEM) at a cell density of 50 to 200 cells per 10-cm dish and allowed to form a colony; (iv) the resulting colonies were treated with trypsin/EDTA in a stainless steel cloning ring to pick up the colonies; (v) the resulting colonies were subjected to cloning 2 to 4 times via limiting dilution, and cells that maintained proliferative capacity and viability were selected; (vi) the selected cells were examined for the expression of type II collagen, which is expressed in chondrocytes, and the expression of type X collagen, which has low expression in undifferentiated chondrocytes, and candidates for the cell lines that maintain the traits of undifferentiated chondrocytes were selected; (vii) the candidate cell lines were subjected to 5 generations of subculture and then were verified to be capable of stably maintaining their properties (e.g., paragraph bridging pages 61-62). The specification teaches that two types of cell lines were obtained using the disclosed procedure: RU-1 and RU-22.

Art Unit: 1636

The clonal selection process used in the present specification does not result in cells that are identical. For example, cells of the RU-1 chondrocyte cell line have a polygonal conformation that stores extracellular matrix, which is a chondrocyte-like morphology, whereas the RU-22 cell line has a very flat configuration with a low extracellular matrix expression level and does not have a chondrocyte-like morphology (e.g., page 63, Example 1, section (5); Figure 1). Although it would have been within the skill in the art at the time the invention was made, to mate the prior art Runx2/Cbfa1 heterodeficient and p53 deficient mice, and isolate cells according to the method disclosed in the specification, it would require undue experimentation to obtain cells with characteristics identical to that of RU-1 and RU-22.

Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. It is noted that RU-1 and RU-22 cell lines have been deposited under the accession numbers FERM-BP-10137 and FERM BP-10138, respectively, at the International Patent Organism Depository of the National Institute of Advanced Industrial Science and Technology under the Budapest Treaty. The specification contains the deposit accession numbers, date of deposit, name and address of the depository, and a description of the deposited material. To meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide a statement that all

Art Unit: 1636

restrictions on the availability to the public of the material so deposited will be irrevocably removed upon granting of a patent.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Kobayashi et al (Biochemical and Biophysical Research Communications, Vol. 273, pages 630-636, 2000; see the entire reference).

Kobayashi et al teach a Runx2/Cbfa1 deficient mouse-derived primary chondrocyte cell culture (e.g., page 633, paragraph bridging columns; Figures 3B and 3D; Table 1).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any



Art Unit: 1636

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kobayashi et al (Biochemical and Biophysical Research Communications, Vol. 273, pages 630-636, 2000; see the entire reference) in view Kamiya (Journal of Bone and Mineral Research, Vol. 17, No. 10, pages 1832-1842, October 2002, cited on the IDS filed 4/20/2006 and provided as pages 1/6-6/6; see the entire reference).

Kobayashi et al teach a Runx2/Cbfa1 deficient mouse-derived primary chondrocyte cell culture (e.g., page 633, paragraph bridging columns; Figures 3B and 3D; Table 1). The cells are derived from the anterior region of calvaria of Runx2/Cbfa1 -/- embryos at embryonic day 18.5 (E18.5) and are induced to differentiate into chondrocytes a culture comprising BMP-2 (e.g., page 632, *Cell preparation and culture conditions*; page 633, *BMP-2 induction of chondrocyte differentiation and inhibition of adipocyte differentiation in Cbfa1-deficient calvarial cells*).

Kobayashi et al do not teach the chondrocytes, where they are derived from a mouse that is p53 deficient in addition to being Runx2/Cbfa1-deficient.

Kamiya et al teach a p53-null mouse and the derivation of chondrocytic cells and chondrocytes from the p53-null mouse (e.g., page 2/6, 1<sup>st</sup> full paragraph; page 2/6, *Cloning of chondrocytic cells and Evaluation of proliferation and differentiation*; pages 3/6-4/6, *Induction of N1511 cells with either BMP/Insulin or PTH/dexamethasone*; page 4/6, *Formation of cartilage nodules and mineralization of N151*). Kamiya et al teach that the chondrocytic cell line

Art Unit: 1636

derived from the p53-null mouse is capable of reproducing the whole process of chondrocyte differentiation, providing an excellent model to study cartilage development, homeostasis and function (e.g., page 5/6, 2nd full paragraph). Further, Kamiya et al teach that p53-deficiency is sufficient to establish immortalized cell lines, because p53 is not present to inhibit proliferation (e.g., page 2/6, 1st full paragraph; page 5/6, 1st full paragraph; page 5/6, 2<sup>nd</sup> full paragraph; paragraph bridging pages 5/6-6/6).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain a chondrocyte derived from a Runx2/Cbfa1-and p53-deficient mouse by mating the Runx2/Cbfa mouse line of Kobayashi et al with the p53 mouse line of Kamiya et al, isolating chondrocytic cells from bone at E18.5, and subjecting the cells to culture conditions to promote the differentiation of the cells to chondrocytes, because both Kobayashi et al and Kamiya et al teach obtaining cells capable of differentiating to chondrocytes in culture from a mouse deficient in a gene.

One would have been motivated to make such a modification in order to receive the expected benefit of providing chondrocytes that are also deficient in p53, resulting in increased proliferation and immortalization in culture, while retaining the ability to differentiate to chondrocytes, as taught by Kamiya et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

### ***Conclusion***

No claims are allowed.

Art Unit: 1636

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.  
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Art Unit 1636

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